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Mycophenolate versus azathioprine as maintenance therapy for lupus nephritis

Dooley *et al.*, *N Engl J Med* 2011; **365**: 1886–1895; doi:10.1056/NEJMoa1014460

Although there is relatively effective induction therapy for severe lupus nephritis, optimal maintenance therapy is still being investigated. Previously, it had been shown that, following short-term induction therapy with intravenous cyclophosphamide (IVC), maintenance therapy with mycophenolate mofetil (MMF) or azathioprine (AZA) was more efficacious than long-term IVC,[1] and in a second study,[2] following an attenuated IVC regimen, MMF was shown to be equally as efficacious as AZA in maintaining remission. Now, we have another study comparing AZA with MMF as maintenance therapy in patients with proliferative lupus nephritis. This is an extension of the previously published Aspreva Lupus Management Study (ALMS),[3] which had shown that MMF was not superior to IVC in inducing remission. In this maintenance study (116 on MMF and 111 on AZA), MMF was superior to AZA with respect to the primary end point, time to treatment failure (hazard ratio, 0.44; 95% confidence interval, 0.25–0.77). MMF was also superior with respect to secondary end points, time to renal flare and time to rescue therapy (hazard ratio, <1.00). Minor treatment-related adverse events were common, with infections and gastrointestinal disorders occurring in more than 95% of the patients in both groups. Serious adverse events occurred in 33% of the patients in the AZA group and in 24% of those in the MMF group, and the rate of withdrawal due to adverse events was higher with AZA than with MMF (40% versus 25%).

The strengths of the ALMS maintenance trial were the large number of patients and the multiethnic cohort. Unanswered questions remain, as pharmacokinetics data were not available and subgroup analysis to see whether particular groups of patients would benefit from AZA was not possible because of sample-size issues, length of therapy, and corticosteroid dose and duration. Regardless, MMF now appears to be an established agent in induction and maintenance therapy for severe lupus nephritis.

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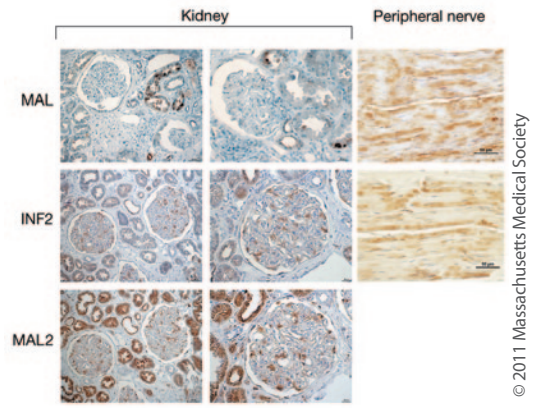
[1] *N Engl J Med* 2004; **350**: 971–980. [2] *Ann Rheum Dis* 2010; **69**: 2083–2089. [3] *J Am Soc Nephrol* 2009; **20**: 1103–1112.

INF2 mutations in Charcot–Marie–Tooth disease with glomerulopathy

Boyer *et al.*, *N Engl J Med* 2011; **365**: 2377–2388; doi:10.1056/NEJMoa1109122

Charcot–Marie–Tooth (CMT) neuropathy is one of the most common forms of inherited neuropathy and can occur as a result of mutations in at least 40 different genes. This disease is characterized by progressive motor neuropathy affecting limb muscles, and patients typically develop sensory abnormalities. CMT neuropathy can occur as a result of either abnormalities of axonal function or abnormal myelination of axons by Schwann cells. Its clinical manifestations can vary considerably, and there have been several reports of proteinuric kidney neuropathy occurring in patients with CMT neuropathy, the most common renal pathologic lesion being focal segmental glomerulosclerosis (FSGS). Until now, the molecular mechanisms linking CMT neuropathy and FSGS pathogenesis were unknown. Since mutations in *INF2* have recently been shown to cause autosomal dominant FSGS, and INF2 can interact with the Rho-GTPase CDC42 and myelin and lymphocyte protein (MAL), which are important factors in myelin formation and maintenance, Boyer *et al.* tested the hypothesis that INF2 may be responsible for cases of CMT neuropathy associated with FSGS. The investigators genotyped INF2 in 16 patients with CMT neuropathy and FSGS who did not have mutations in genes commonly associated with CMT neuropathy. The authors identified nine new heterozygous mutations in 12 of the 16 patients who presented with an intermediate form of CMT neuropathy as well as a glomerulopathy with FSGS on kidney biopsy. All mutations were located in exons encoding the diaphanous-inhibitory domain of INF2. Immunostaining demonstrated that INF2 was present in Schwann-cell cytoplasm and podocytes. Moreover, the authors demonstrated that INF2 colocalizes and interacts with MAL in Schwann cells (Figure). Mutations in *INF2* disrupted the INF2–MAL–CDC42 pathway, resulting in cytoskeleton disorganization, enhanced INF2 binding to CDC42, and mislocalization of INF2, MAL, and CDC42.



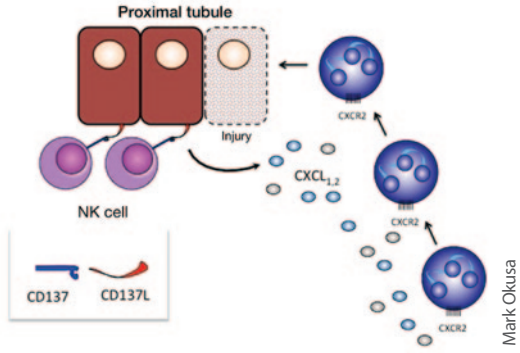
MAL, INF2, and MAL2 proteins in normal human kidney specimens and peripheral nerve biopsy specimens. The serial sections shown suggest that INF2 colocalizes with MAL2 in podocytes and MAL in Schwann cells.

This study demonstrates that INF2 is important for normal function of podocytes and Schwann cells and that mutations in *INF2* can cause FSGS-associated CMT neuropathy. Also, this paper is particularly interesting because although several podocyte proteins have been demonstrated to have important roles in the biology of neuronal cells, this is the first report of a podocyte protein that influences neuronal function via its role in Schwann cells. Perhaps these results should not surprise, given that both podocytes and Schwann cells use highly specialized cytoskeletal architecture to wrap capillaries and neurons, respectively.

Michael Ross

Reverse signaling through the costimulatory ligand CD137L in epithelial cells is essential for natural killer cell–mediated acute tissue inflammation

Kim *et al.*, *Proc Natl Acad Sci USA* 2012; **109**: E13–E22; doi:10.1073/pnas.1112256109



The costimulatory ligand CD137L in epithelial cells is essential for natural killer (NK) cell–mediated acute tissue inflammation. Following ischemia-reperfusion, NK cells infiltrate into the kidney and through cell surface CD137 stimulate proximal tubule epithelial cells through their cell surface ligand CD137L. CD137 signaling leads to the production of chemokines CXCL1 and CXCL2 (CXCL1,2) and chemotaxis of neutrophils. Neutrophils participate in tissue inflammation and injury.

The innate immune system is composed of inflammatory cells such as dendritic cells, macrophages, neutrophils, natural killer T cells, and natural killer (NK) cells that contribute to an inflammatory cascade leading to renal epithelial-cell apoptosis and necrosis following kidney ischemia–reperfusion injury (IRI) (Figure). Dying cells release endogenous molecules called damage/danger-associated molecular patterns that activate the immune system. These molecules activate immune cells, resulting in the recruitment of neutrophils, a key mediator of tissue injury.

Following kidney IRI, NK cells directly kill tubular epithelial cells (TECs) through interactions between the NKG2D receptor on NK cells and Rae-1 on TECs in a perforin-dependent manner. Kim *et al.* add new insight into the role of NK cells in kidney IRI by demonstrating the critical role of CD137L–CD137 signaling. In classical adaptive immunity, CD137L expressed on antigen-presenting cells can costimulate CD137 on T cells, but there are also data that suggest that CD137L–CD137 signaling is important in innate immunity. Through reverse signaling, antigen-presenting cells expressing CD137L can be activated by NK-cell CD137 to secrete cytokines and chemokines. The authors demonstrated that CD137L is expressed on TECs, and the absence of CD137 in mice reduced kidney IRI. Recombinant CD137 crystallizable fragment (Fc) fusion protein engages TEC CD137L to secrete CXCL1 and CXCL2 and, when administered systemically, induces more injury following IR. The proof *in vivo* that epithelial-cell CD137L activation induced injury comes from the study in which wild-type TECs were implanted in CD137L knockout mice below the renal capsule. In CD137L knockout mice, which are normally protected from IRI, implantation of wild-type TECs led to IRI-induced NK-cell CD137 expression, and transfer of NK cells into CD137 knockout mice reconstituted injury and induced high levels of functional CXCL1 and CXCL2. Thus, these results reveal that NK cells, through CD137L–CD137 reverse signaling, promote tissue injury by enhancing chemokine production, leading to neutrophil infiltration and inflammation. This study defines a novel mechanism that may be exploited therapeutically.

Mark Okusa

Rapid, persistent action of Tregs depends on blockade of intracellular calcium release

Schmidt *et al.*, *Sci Signal* 2011; **4**: ra90; doi:10.1126/scisignal.2002179

Regulatory $CD4^+CD25^+$ FOXP3-expressing T cells (Tregs) have been the object of extensive research in recent years, but the precise molecular mechanisms of their action remain to be fully elucidated. With respect to the kidney, Tregs may have beneficial effects in transplant rejection, immune-mediated glomerulonephritis, and renal cancer, by directly inhibiting the proliferation of $CD4^+CD25^-$ T lymphocytes and their production of effector cytokines. In their study, Schmidt and collaborators describe a rapid but persistent mechanism of inhibition of cytokine production by Tregs on $CD4^+CD25^-$ T lymphocytes that relies on inhibition of calcium release from intracellular stores.

The authors demonstrate that preactivated Tregs need only a very short period (30–45 minutes) of coculture with $CD4^+CD25^-$ T lymphocytes to inhibit calcium signaling and consequently suppress their signaling machinery. Suppressed $CD4^+CD25^-$ T lymphocytes are unable to activate NF-κB and NFAT1 signaling pathways, which consequently prevents the expression of cytokine-encoding genes. In contrast, Ca^{2+}-independent events, such as T-cell receptor (TCR)-proximal signaling and activation of the transcription factor AP-1, are not affected. Therefore, these results elucidate a previously unrecognized and rapid mechanism of Treg-mediated suppression and suggest that at least two different mechanisms of suppression of human $CD4^+CD25^-$ T lymphocytes might operate. First, rapid suppression of Ca^{2+}, NFAT, and NF-κB signaling might result in inhibition of cytokine production, which is maintained upon removal of Tregs and seems to be independent of cytotoxic T-lymphocyte-associated antigen 4 (CTLA-4) and antigen-presenting cells. Second, suppression of the proliferation of human $CD4^+CD25^-$ T lymphocytes might require prolonged contact with Tregs and may be independent of Ca^{2+} signaling and the suppression of cytokine production.

Several questions remain open. Most importantly, the exact signaling events that lead to inhibition of Ca^{2+} release remain to be determined. Also, CTLA-4 and TCRs excluded, the receptor that mediates these rapid effects remains to be shown.

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